Soy Connection Fact Sheet

SOY + BREAST CANCER

CLINICAL DATA | EPIDEMIOLOGIC DATA | SUMMARY AND CONCLUSIONS

Soyfoods in the diet of women with breast cancer.

Introduction

Interest in the protective effects of soyfoods against breast cancer began three decades ago[1] and can be attributed primarily to two observations. The first observation is the historically low breast cancer mortality rates in soyfood-consuming Asian countries.[2] The second observation is the potential for soybean isoflavones to function as anti-estrogens.[3] Foods made from soybeans are uniquely rich sources of isoflavones, which are diphenolic, nonsteroidal molecules.[4] These soybean constituents are classified as both phytoestrogens and selective estrogen receptor modulators (SERMs).[5]

SERMs can function as estrogen receptor (ER) agonists, ER antagonists or have no effects at all in tissues that possess ERs. The preference for isoflavones to bind to and activate ERβ in comparison to ERα is thought to account for their SERM-like properties.[5] When activated, these two receptors can have very different and sometimes even opposite physiological effects. For example, in the breast, activation of ERβ is thought to inhibit the proliferative effects of ERα activation.[6] In contrast to isoflavones, estrogen has equal affinity for both receptors.

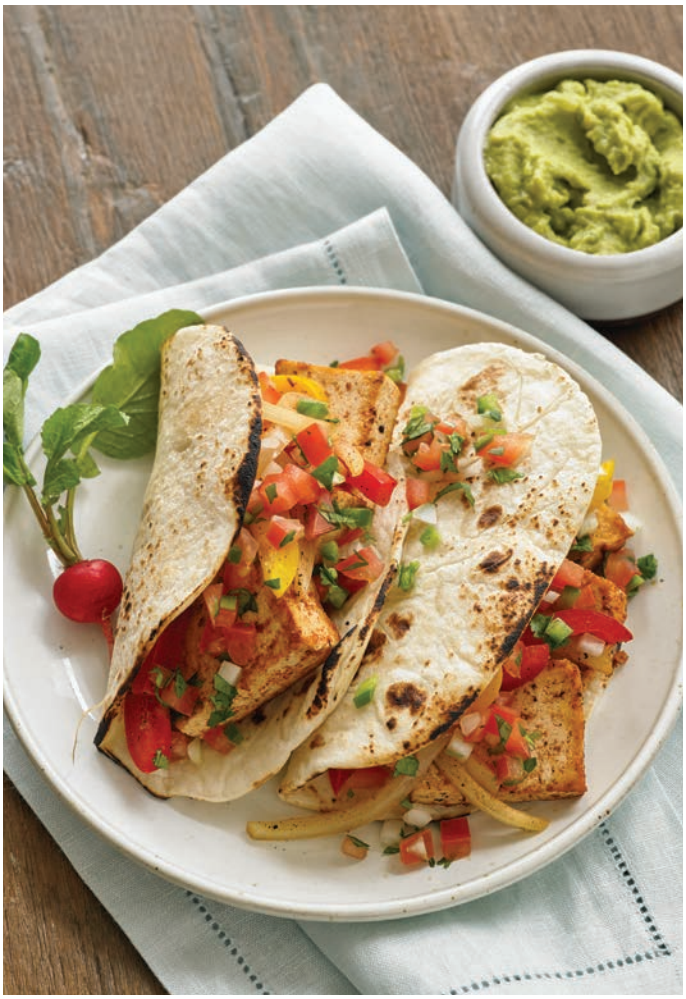
Epidemiologic research indicates soy consumption is associated with an approximate one-third reduction in risk of developing breast cancer.[7] However, several lines of evidence suggest that for soy to reduce breast cancer risk, consumption must occur during childhood and/or adolescence. Case-control studies indicate that the consumption of just one to two servings of soy during this period may reduce breast cancer risk by as much as 60 percent.[8-10] Isoflavones appear to change the cells in the developing breast that makes them permanently less likely to transform into cancer cells. The notion that early soy intake reduces breast cancer risk is consistent with current understanding that exposures and events

during the first 20 years of life profoundly impact risk of developing breast cancer.[11]

Despite the proposed breast cancer preventive effects, there has been concern that soyfoods, because they contain isoflavones, worsen the prognosis of women with breast cancer and increase the risk of developing breast cancer in women who are at high risk for this disease. The soy breast cancer controversy is based almost exclusively on a series of rodent studies that began to be published in the late 1990s, which showed that isoflavones stimulate the growth of existing estrogen-sensitive mammary tumors in athymic ovariectomized mice.[12,13] Of the three isoflavones in soybeans, genistein, daidzein and glycitein, it is primarily genistein that stimulates tumor growth in this model.

There are well-known limitations to animal studies but in the case of soy-related research, rodents appear to be of especially limited value for providing insight about soyfoods because they metabolize isoflavones so differently than humans.[14] Furthermore, it was shown in 2011, that just slightly tweaking the above referenced athymic ovariectomized rodent model in what is an arguably a more physiological direction, causes a complete loss of the tumor-stimulatory effect of genistein.[15]

More importantly, as discussed below, over the past decade or so, human research indicates not only that women with breast cancer can safely consume soyfoods but may benefit by doing so. It is noteworthy that the extent to which estrogen therapy increases breast cancer risk is unclear. In fact, in the Women's Health Initiative trials, estrogen therapy led to a statistically significant decreased risk of dying from breast cancer whereas estrogen plus progestin therapy led to a significant increase.[16] Thus, it is the progestin component of hormone therapy, much more than estrogen, that is problematic. Soy does not exert progestin-like effects.



Clinical Data

No intervention study has examined the impact of soy consumption on breast cancer recurrence and/or mortality. For this reason, it must be acknowledged that data that are able to definitively resolve the soy breast cancer controversy do not exist. However, the impact of soy on several established markers of breast cancer risk, including mammographic density[17,18] and breast cell proliferation[19] has been studied extensively. The results of this research are extremely reassuring in that it shows even when isoflavone exposure greatly exceeds typical Japanese intake, which is ~40 milligrams per day (mg/d),[20] breast tissue is not adversely affected. Not surprisingly, this is the conclusion reached by the European Food Safety Authority after a multi-year comprehensive evaluation of the literature.[21]

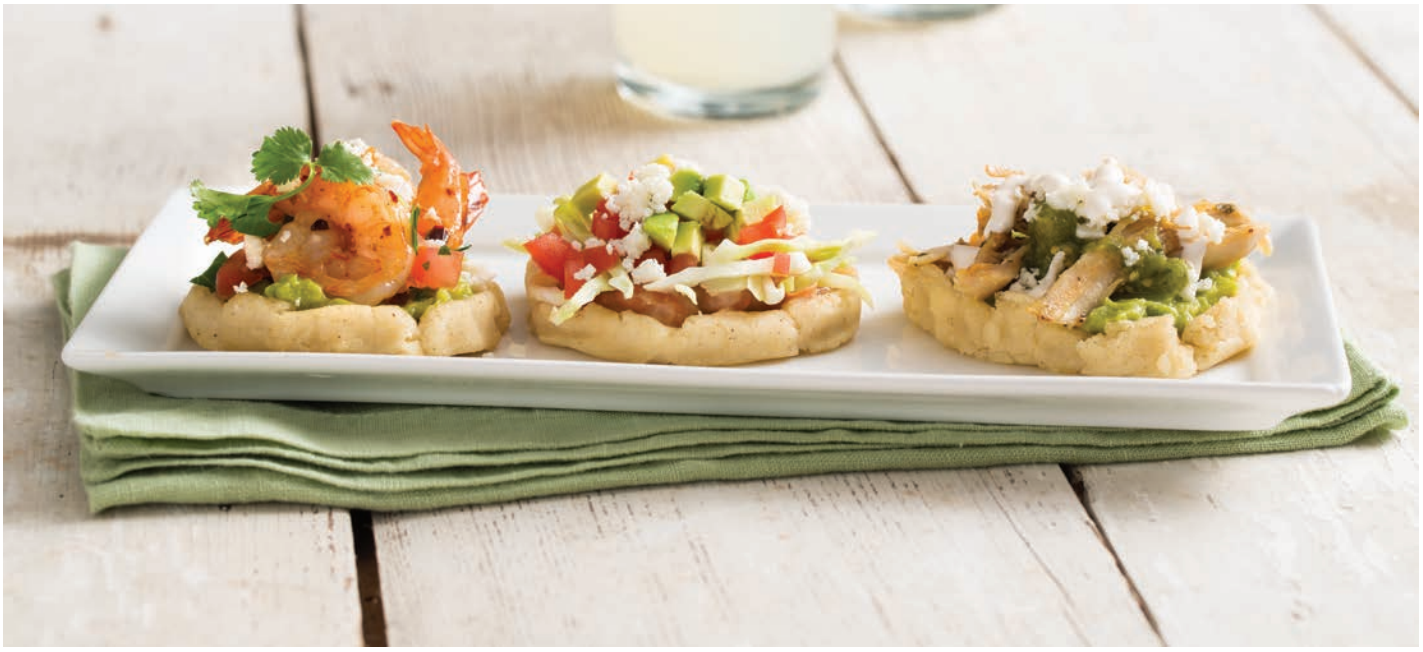
Mammographic Density

Variations in percent mammographic density reflect variations in the amounts of collagen and number of epithelial and non-epithelial cells in the breast. Extensive mammographic density is associated with a markedly increased risk of invasive breast cancer.[17] In 2009, a meta-analysis by Hooper et al.[22] concluded that isoflavone intake does not alter breast tissue density in postmenopausal women (the group proposed as being at risk from isoflavone exposure) but may cause a small increase in premenopausal women. However, the clinical significance of this latter finding was deemed unclear and statistical significance was lost in one of three sensitivity analyses. The results in postmenopausal women are aligned with two subsequently published one-year studies. In one, Wu et al.[23] found no evidence that 50 mg/d isoflavones affect breast MRI fibroglandular tissue density or mammographic density in high-risk women and previously treated breast cancer patients. Additionally, a Greek study of postmenopausal women that intervened with a soy extract found no effect on mammographic density, although this was also true for low-dose hormone therapy.[24]

Breast Cell Proliferation

A better predictor of breast cancer risk than mammographic density is in vivo breast cell proliferation.[25] The most widely practiced measurement of proliferation involves immunohistochemical detection of the nuclear non-histone protein Ki67, which is thought to be involved in ribosomal RNA synthesis.[26,27] The fraction of actively cycling cells in normal breast tissue appears to represent a marker for breast cancer risk assessment.[19] In addition, Ki-67 level is considered a valuable biomarker in breast cancer patients that can be used in treatment and follow-up.[28] Estrogen plus progestin therapy, which observational studies show is associated with a marked increased risk of breast cancer, has been shown to increase proliferation four to 10-fold within just 12 weeks.[29-31]

In contrast to the proliferative effects of combined hormone therapy, none of the six studies that evaluated the effects of isoflavones on in vivo breast cell proliferation showed an increase in comparison to the control or placebo group.[32-37] These studies involved healthy women, women at high-risk of developing breast cancer and breast cancer survivors. The duration of these



studies ranged from two weeks[32] to one year.[34] Daily isoflavone intake – expressed in aglycone equivalents – ranged from 36[35] to 235[36] mg. For comparison, one serving of a traditional soyfood (e.g., 100 g tofu or 250 ml soymilk) contains ~25 mg isoflavones and mean daily intake among older adults in Japan ranges from 30 to 50 mg.[20] In the study by Palomares et al.,[34] which involved breast cancer survivors, the contralateral breast was used to assess cell proliferation and in the study by Sartipour et al.,[33] the ratio of the number of apoptotic to mitotic cells was used as an assessment of proliferation.

It is noteworthy that in the studies by Shike et al.[37] and Khan et al.,[36] women were exposed to approximately 62 mg/d and 150 mg/d genistein, respectively, amounts provided by approximately five and 12 servings of traditional soyfoods, respectively. Thus, untoward effects on the breast were not noted, even in response to isoflavone intakes that exceed those which can reasonably be consumed via soyfoods. It is also noteworthy that three of the six studies found gene expression was modified in a manner suggestive of a proliferative effect and an increased breast cancer risk, which might be expected from estrogen exposure, and yet proliferation was unaffected.[32,36,37]

Prospective Epidemiologic Data

Over the past 10 years, five prospective epidemiologic studies, three from China[38-40] and two from the U.S.,[41,42] have evaluated the impact of post-diagnosis soy intake on the prognosis of breast cancer survivors. The results of these studies are not only supportive of the safety of soyfood consumption but suggest it significantly reduces breast cancer recurrence and breast cancer specific mortality. In 2012, based on the epidemiologic data, the American Institute for Cancer Research (AICR)[43] and the American Cancer Society[44] concluded that breast cancer patients can safely consume soyfoods.

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In 2018, a report from the AICR and the World Cancer Research Fund concluded that post-diagnosis soy intake may improve the survival of breast cancer patients.[45]

The key epidemiologic research addressing the impact of soy intake on the prognosis of breast cancer survivors was published in 2013. Chi et al.[46] meta-analyzed the results of five prospective studies, three from China and two from the U.S. These studies involved over 11,000 women who were followed for between approximately four and seven years. When comparing high soy intake (~2 servings per day) with low soy intake (<½ serving per day) after a diagnosis of breast cancer, high soy intake was associated with a 16% reduction in mortality and a 26% reduction in recurrence. Both of these findings were statistically significant. Furthermore, the beneficial effect of post-diagnosis soy intake was apparent in Chinese women to the same extent as American women. Also, soy benefited both both ER+ and ER- breast cancer patients.

There is no obvious mechanistic explanation for the beneficial effects of post-diagnosis soy intake given that the relevant clinical data found soy/isoflavone intake did not affect markers of breast cancer risk. It may be that soy/isoflavone exposure exerts effects undetected by changes in mammographic density or cell proliferation. For example, there is research suggesting soyfoods could inhibit angiogenesis (the growth of blood vessels)[48,49] and metastasis.[50,51,52]

Summary and Conclusions

The human research overwhelmingly indicates that breast cancer patients can safely consume soyfoods. This conclusion has been reached by four independent health organizations.

In the prospective epidemiologic studies discussed above, isoflavone exposure occurred via the consumption of soyfoods. In contrast, the clinical studies intervened primarily with soy protein or isoflavone supplements. Given all the data, the evidence indicates that soyfood intake recommendations for breast cancer survivors do not differ from those for healthy women. In the SBCSS, post-diagnosis soy protein intake was associated with benefit even when intake exceeded 20 g/d. Additionally, in the fourth quartile, the isoflavone intake cutoff in the SBCSS was >62.68 mg/d. Women in this group were consuming approximately three servings of soyfoods per day. However, in Japan and high soy-consuming regions within China such as Shanghai, mean soyfood intake is closer to 1½ to 2 servings per day.

Clinical Studies Evaluating the Effects of Soy Isoflavone Exposure and Breast Cell Proliferation and Apoptosis

AUTHOR/YEAR/ (REFERENCE)	MENOPAUSAL STATUS	BREAST CANCER STATUS	PERCENT ER+ PATIENTS	(N)[1]	STUDY DURATION, MEAN (RANGE)	INTERVENTION PRODUCT	TOTAL ISOFLAVONE EXPOSURE (MG/D)[2]	PROLIFERATION	APOPTOSIS
Hargreaves/ 1999/(17)	Premenopausal	Mixed[3]	Not indicated	28 Soy 53 Control	~14 days (8-14)	Textured vegetable protein	45	No change	No change
Sartippour/ 2004/(18)	Postmenopausal	Yes	84	17 Soy 26 Control	23 days (13-45)	Tablets	120	No change	No change
Palomares/ 2004/(19)	Postmenopausal	Yes	74	9 Soy 9 Control	11.7 months	Tablets	100	No change[4]	Not Evaluated
Cheng/ 2007/(20)	Postmenopausal	No	Not applicable	26 Soy 25 Control	12 weeks	Tablets	36	No change	Not Evaluated
Khan/ 2012/(21)	Pre- and post-menopausal[5]	High risk[6]	Not applicable	49 Soy 49 Control	6 months	Tablets	235 (150 genistein)	No change	No change
Shike/ 2014/(11)	Postmenopausal	Yes	85	54 Soy 50 Control	14 days (7-30)	Isolated soy protein	103 (62 genistein)	No change	No change

[1] Based on the number evaluated for proliferation [2] Exressed as aglycone equivalent weight [3] Fibroadenoma (38), invasive ductal breast cancer (13), fibocystic masses (9), ductectasia (6), sclerosing adenosis (3), ductal carcinoma in situ (3), lipoma (1), assessor breast removal (1) [4] Samples were normal tissue from contralateral breast [5] n=45 postmenopausal, 53 postmenopausal [6] Women with a history of unilateral risk breast cancer or with a 5-year Gail or Claus risk estimate ≥1.66% for women older than 40 years, ≥1.0% for those aged between 30 and 39, and ≥0.1% for women aged between 20 and 29.

Key Takeaways for Patient Care

1	Soyfoods are uniquely-rich sources of isoflavones.
2	Isoflavones are classsified as phtoestrogens but different from the hormone estrogen at both the molecular and clinical level.
3	The estrogen-like activity of isoflavones has raised concern that soyfoods may adversely affect the prognosis of women with breast cancer.
4	Limited clinical data show that exposure to high-doses of isoflavones may affect the expression of genes in breast tissue involved in controlling cell proliferation.
5	Extensive clinical data show that exposure to high-dose isoflavones does not affect the rate at which breast cells replicate in healthy and in woomen who have been diagnosed with breast cancer.
6	Extensive prospective epidemiologic data from China and the United States show that the consumption of soyfoods after a diagnosis of breast cancer reduces breast cancer-specific mortality and tumor recurrence.
7	The clinical and epidemiologic data are consistent with the positions of the American Cancer Society and the American Institute for Cancer Research which are that women with breast cancer can safely consume soyfoods.

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Soy Connection, on behalf of the United Soybean Board (USB), is a collaboration of health, nutrition and food industry experts with U.S. soybean farmers to educate on the benefits of U.S.-grown soy, including heart-healthy soybean oil and soyfoods. USB's 73 farmer-directors work on behalf of all U.S. soybean farmers to achieve maximum value for their soy checkoff investments. These volunteers invest and leverage checkoff funds in programs and partnerships to drive soybean innovation beyond the bushel and increase preference for U.S. soy. That preference is based on U.S. soybean meal and oil quality and the sustainability of U.S. soybean farmers. As stipulated in the federal Soybean Promotion, Research and Consumer Information Act, the USDA Agricultural Marketing Service has oversight responsibilities for USB and the soy checkoff.

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